REMARKS

This is a full and timely response to the Advisory Action mailed April 17, 2009, submitted herein with a Request for Continuing Examination. Reconsideration and allowance of the application and all presently pending claims are respectfully requested.

Present Status of Patent Application

Upon entry of this Amendment, claims 1-48 are pending in the present application. Claims 29, 30, and 46-48 are withdrawn from consideration. Claims 1 and 31 are amended herein.

The prior art made of record has been considered, but is not believed to affect the patentability of the presently pending claims. Applicants believe that no new matter has been added and that a new search is not necessary.

Response to Applicants' Arguments

The Examiner stated in the Final Office Action mailed January 29, 2009 at pp2-3 that:

> "With respect to assertion A, Applicants arguments are not found persuasive. Claims 1 and 3 1 have been amended to make them recite the limitation that the components are distinct. But what does such a limitation mean? Distinct according to the definition has a variety of meanings. The definition of 'distinct' is applied according to the definitions set forth by Dictionary.com (Exhibit A). Distinct means, 'not alike', 'dissimilar', or 'separate'. It is the opinion of the Examiner that the composition of *Phillips* teaches distinct components in all of these senses. In the sense that the components are 'not alike', *Phillips* obviates the instant claims. Each component has distinct properties. For examples, one PPI is released immediately, another PPI is enterically coated and slowly released, and there is a basic substance which is separate from both of the previous actives. Each of these components has a different physical property from the other. Thus, the populations of ingredients in the composition would necessarily be distinct according to this definition. In the sense that the components are 'separate', it is the position of the Examiner that *Phillips* meets this limitation too. While it may be true that components are admixed together, they still exist as 'separate' entities within the pharmaceutical mixture. Applicant is directed to Example VI of *Phillips*. Applicants arguments are not found persuasive."

Applicants have herein amended claims 1 and 31 to clearly state that **each** of the three (claim 1), or four (claim 31), components of the claimed compositions is **each** a population of beads, a population of pellets, a population of tablets, a population of granules, or a combination thereof. The amendments to the claims have been made for clarity. Accordingly, Applicants respectfully assert that the populations of pharmaceutical actives are clearly defined in the

amended claims submitted herein, and respectfully request that the Examiner's comments regarding such now be withdrawn.

Claim rejections under 35 U.S.C. §103(a)

In the Advisory Action mailed April 17, 2009, the Examiner stated Claims 1-28 and 31-45 were rejected under 35 USC §103(a) as being unpatentable over *Phillips* (US2002/0045646) and *Bergstrand* (US 5,817,338). The Examiner has asserted that the previous response to this rejection was unpersuasive.

Claim 1 and claims 2-28 dependent therefrom

In the Office Action, claims 1-28 and 31-45 were rejected under 35 USC § 103(a) as being unpatentable over *Phillips* (US2002/0045646) and *Bergstrand* (US 5,817,338). Applicants respectfully traverse this rejection.

Claim 1 is an independent claim. This claim is directed to an oral pharmaceutical composition comprising three populations of pharmaceutical actives provided in a capsule. Claim 1, as amended herein, clearly recites three populations, (i), (ii), and (iii), where each population is a population of beads, pellets, tablets, granules, ***or*** a combination thereof.

The present claims are directed to oral pharmaceutical formulations in capsule form. Each capsule comprises first and second populations of pharmaceutical actives and at least one population of a basic substance. Each of the three populations is separately formulated in beads, pellets, tablets, granules, or combinations thereof. Accordingly, the claimed formulations can provide multiple site specific delivery of the pharmaceutical actives at rapid, delayed, and/or sustained release rates into the plasma. As is discussed in the background of the present application, there has been a long-felt need to provide controlled release acid-labile pharmaceutical actives in capsule form.

The present disclosure and claims addresses this need by separately formulating each population of actives and the basic substance into beads, pellets, tablets, granules, or combinations thereof. The separate populations of the beads, pellets, tablets, granules, or combinations thereof are then provided together in a capsule. Thus, as claimed in amended claim 1, the three populations (two pharmaceutical actives and a basic substance) are maintained separately and distinctly (as opposed to two or more of these agents being admixed

when co-milled as a powder), yet are co-administered within a single capsule. Such a multi-functional capsule is not taught or suggested in the cited references.

The Examiner has alleged that *Phillips* discloses a tablet "comprising compressed granules of omeprazole [*sic*] and free sodium bicarbonate as well as enterically coated omeprazole granules" (emphasis added). Even if *Phillips* does disclose such a tablet, it is not what is presently claimed. The present claims are directed to capsules. The claimed capsules comprise three separate populations of ingredients (two pharmaceutical actives and a basic substance) that are **each** in the form of beads, pellets, tablets, granules, or combinations thereof. One population comprises a pharmaceutical active releasable at a first rate, one population comprises a pharmaceutical active releasable at a second rate, and one population is a basic substance.

In Example VI, to which it is believed the Examiner is referring to in the objection, *Phillips* mixes omeprazole **powder** with sodium bicarbonate. The mixture is compressed to form the inner core of a **tablet**. The inner core is then coated with an outer core layer of enterically coated omeprazole granules. The inner core of the *Phillips* embodiment does **not** comprise compressed **granules** of omeprazole, as the Examiner alleges. Instead, it comprises an **admixture** of omeprazole **powder** and sodium bicarbonate, which is compressed to form the core. Powder particles cannot be considered equivalent to granules, since *Phillips* specifically teaches in paragraphs [99] to [102] how granules are formed **from** powders. This contrasts with the subject matter as presently claimed in claim 1, and dependent claims therefrom, where each pharmaceutical active and the basic substance of the encapsulated product is **individually** formed as granules before introducing into the capsule, *Phillips* clearly teaches intimately admixing one pharmaceutical active and the basic substance into a single population of milled powder before contacting with the second pharmaceutical active.

If the Examiner asserts that the inner core, as taught by *Phillips*, is arguably itself a tablet, it is asserted that the inner core is, however, not a "**population** of tablets" as is presently claimed. It is a single tablet comprising omeprazole and sodium bicarbonate. Additionally, a separate population of a basic substance, formulated in beads, granules, pellets, or tablets, is missing from the tablet of Example VI, since the omeprazole and sodium bicarbonate **powders** are **admixed together** as a single milled population prior to compression into a tablet form. The outer core layer of the tablet of Example VI of *Phillips* does arguably comprise a population of

omeprazole granules; however, there are no additional **populations** of granules, tablets, pellets, or beads in the tablet of Example VI.

Furthermore, it is respectfully submitted that the presently claimed composition is formulated in a capsule. Example VI of the cited *Phillips* reference is clearly directed to a compressed tablet. In fact, capsules are only briefly mentioned by *Phillips* and it is simply taught that omeprazole can be formulated in capsules "by methods well known to those skilled in the art" (paragraph [0075] of *Phillips*). *Phillips* provides two specific examples of capsules, and in both cases the basic substance is present within the capsule in **powder** form (paragraphs [0233] and [0450] of *Phillips*) and is not present as a population of beads, tablets, granules, pellets, or combinations thereof, as claimed in the present application.

It is respectfully submitted, therefore, that, at most, *Phillips* discloses a "two-part tablet" and briefly mentions a two-part capsule (paragraph [0036] of *Phillips*), wherein the basic substance is simply provided in powder form. This stands in stark contrast to the presently claimed capsule that comprises at least **three** distinct populations of beads, pellets, granules, tablets, or combinations thereof: the population of the first pharmaceutical active; the population of the second pharmaceutical active; and the population of the basic substance. In other words, the presently claimed capsules comprise **three or more parts** and the claims specifically recite that the three or more parts (i.e., populations) are **each** individually formulated as beads, pellets, tablets, granules, or combinations thereof. This is **not** taught or suggested by *Phillips*.

Bergstrand has only been relied upon for disclosing a separating layer and, for at least this reason, does not overcome the deficiencies of *Phillips* with respect to the Examiner's obviousness objection. While *Bergstrand* may teach that an alkaline layer between a PPI and an enteric coat may protect the PPI, Applicants fail to see how this relates to the contents of the capsules of the claims of the present application. Therein, the contents include a population of enteric coated PPI **granules, tablets, pellets, or beads.** Only **this** component of the presently claimed capsule preparations equates in any way with the PPI preparations as taught by *Bergstrand* that requires an alkaline layer when the PPI is enterically coated. The teachings of *Bergstrand* do **not** relate in any way to the **individual** PPI and basic substance populations of the presently claimed formulations, which are individually **granules, tablets, pellets, or beads.**

For at least the above-described reasons, it is respectfully submitted that *Phillips*, alone or in combination with *Bergstrand*, does not teach or suggest each and every feature of the

presently claimed invention, wherein there are first and second populations of a pharmaceutical active and a population of a basic substance, wherein **each** of the populations is separately formulated in beads, pellets, tablets, granules, or combinations thereof and the populations are provided together in a capsule. It is respectfully requested that this rejection under 35 USC §103(a) be withdrawn.

Claim 31 and claims 32-45 dependent therefrom

In the Office Action, claims 1 to 28 and 31 to 45 were rejected under 35 USC § 103(a) as being unpatentable over *Phillips* (US2002/0045646) and *Bergstrand* (US 5,817,338). Applicants respectfully traverse this rejection.

Claim 31 is an independent claim. This claim is directed to an oral pharmaceutical composition comprising multiple populations provided in a capsule. Claim 31, as amended herein, clearly recites that the four populations (i), (ii), (iii), and (iv), are each individually a population of beads, of pellets, of tablets, of granules, ***or*** a combination thereof.

The present claim 31, and claims dependent therefrom, are directed to oral pharmaceutical formulations in capsule form. Each capsule comprises first and second populations of pharmaceutical actives and at least two populations of basic substances. Each of the four populations (two pharmaceutical actives, at least one of which is enterically coated, and two basic substances, at least one of which is also enterically coated) is separately formulated in beads, pellets, tablets, granules, or combinations thereof. Accordingly, the claimed formulations can provide multiple site specific delivery of the pharmaceutical actives at rapid, delayed, and/or sustained release rates into the plasma. As is discussed in the background of the present application, there has been a long-felt need to provide controlled release acid-labile pharmaceutical actives in capsule form.

The present disclosure addresses this need by separately formulating each population of actives and the basic substance into beads, pellets, tablets, granules, or combinations thereof. The separate populations of the beads, pellets, tablets, granules, or combinations thereof are then provided together in a capsule. Thus, as claimed in claim 31, and claims dependent therefrom, the four populations (two pharmaceutical actives, at least one of which is enterically coated, and two basic substances, at least one of which is also enterically coated), are maintained separately and distinctly, as opposed to two or more of these agents being admixed

co-milled as a powder, yet are co-administered within a single capsule. Such a multi-functional capsule is not taught or suggested in the cited references.

The Examiner has alleged that *Phillips* discloses a tablet "comprising compressed granules of omeprazole [*sic*] and free sodium bicarbonate as well as enterically coated omeprazole granules" (emphasis added). Even if *Phillips* does disclose such a tablet, it is not what is presently claimed. The present claim 31 and claims dependent therefrom are directed to capsules. The claimed capsules comprise four separate populations of ingredients (two pharmaceutical actives and two basic substances) that are **each** in the form of beads, pellets, tablets, granules, or combinations thereof. One population comprises a pharmaceutical active releasable at a first rate, one population comprises a pharmaceutical active releasable at a second rate and is enterically coated, one population is a basic substance, and one population is a basic substance enterically coated.

In Example VI, to which it is believed the Examiner is referring to in the objection, *Phillips* mixes omeprazole **powder** with sodium bicarbonate. The mixture is compressed to form the inner core of a **tablet**. The inner core is then coated with an outer core layer of enterically coated omeprazole granules. The inner core of the *Phillips* embodiment does **not** comprise compressed **granules** of omeprazole, as the Examiner alleges. Instead, it comprises an **admixture** of omeprazole **powder** and sodium bicarbonate, which is compressed to form the core. Powder particles cannot be considered equivalent to granules, since *Phillips* specifically teaches in paragraphs [99] to [102] how granules are formed **from** powders. Whereas each pharmaceutical active and the basic substance of the encapsulated product as claimed in the present application is **individually** formed as granules before introducing into the capsule, Plillips clearly teaches intimately admixing one pharmaceutical active and the basic substance into a single population before contacting with the second pharmaceutical active.

If the Examiner asserts that the inner core is arguably itself a tablet, it is asserted that the inner core is, however, not a "**population** of tablets" as is presently claimed. It is a single tablet comprising omeprazole and sodium bicarbonate. Additionally, a separate population of a basic substance, formulated in beads, granules, pellets, or tablets, is missing from the tablet of Example VI, since the omeprazole and sodium bicarbonate **powders** are **admixed together** as a single population prior to compression into a tablet form. The outer core layer of the tablet of Example VI does arguably comprise a population of omeprazole granules; however, there are no additional **populations** of granules, tablets, pellets, or beads in the tablet of Example VI.

Furthermore, it is respectfully submitted that the presently claimed composition is formulated in a capsule. Example VI of the cited *Phillips* reference is clearly directed to a compressed tablet. In fact, capsules are only briefly mentioned by *Phillips* and it is simply taught that omeprazole can be formulated in capsules "by methods well known to those skilled in the art" (paragraph [0075] of *Phillips*). *Phillips* provides two specific examples of capsules, and in both cases, the basic substance is present within the capsule in **powder** form and is not present as a population of beads, tablets, granules, pellets, or combinations thereof (paragraphs [0233] and [0450] of *Phillips*).

It is respectfully submitted, therefore, that, at most, *Phillips* discloses a "two-part tablet" and briefly mentions a two-part capsule (paragraph [0036] of *Phillips*), wherein the basic substance is simply provided in powder form. This stands in stark contrast to the presently claimed capsule that comprises at least **four** distinct populations of beads, pellets, granules, tablets, or combinations thereof: the population of the first pharmaceutical active; the population of the second, enterically coated, pharmaceutical active; the population of one basic substance, and the population of the second basic substance, which is also enterically coated. In other words, the capsules presently claimed in claim 31 comprise **at least four parts (populations)** and the claims specifically recite that the three or more parts (i.e., populations) are **each** individually formulated as beads, pellets, tablets, granules, or combinations thereof. This is **not** taught or suggested by *Phillips*.

The populations are further clarified upon a reading of the specification, for example page 8, line 21 to page 9, line 11 which reads as follows:

> "The pharmaceutical capsule of the invention is made such that each population of beads, pellets, tablets or granules has a distinct physiological function.
>
> The function of the first population, comprising the pharmaceutically active substance, such as a proton pump inhibitor compound (PPI), that is rapidly releasable, is to deliver the pharmaceutical active beginning in the stomach. This is made possible due to the presence of an optional excipient and by the stable environment created by the elevated pH environment of the stomach brought about by the rapid disintegration and dissolution of the population of basic substance whose function is to rapidly deliver basic material to the stomach, which allows for precise control of the stomach pH to more than about 4.0 and less than about 7.0 and, typically, less than about pH 6.3. This pH can also be achieved in less than about 1 hour.
>
> The function of the second population, comprising the pharmaceutical active substance, such as a proton pump inhibitor compound (PPI), that is released

slower than that of the first population, is to deliver another quantity of the pharmaceutical active between the duodenum and just past the ileocecal junction. This is possible due to the presence of an excipient that controls the release of the pharmaceutical active and the choice and quantity of the basic substance delivered in the stomach by the population of basic substance. The pharmaceutical active substance of the second population may be released in a delayed and/or sustained manner."

Even further examples of the description of multiple populations are provided in the specification, for example at page 11, lines 10 to 32 and throughout the Examples.

In contrast, neither *Phillips* nor *Bergstrand* teach or otherwise suggest a capsule comprising at least four populations, where each population is a population of beads, of pellets, of tablets, of granules, ***or*** a combination thereof. In the Office Action mailed January 29, 2009, Example VI of *Phillips* is referenced by the Examiner. Example VI of *Phillips* discloses tablets that are compounded using known methods by forming an inner core of omeprazole powder mixed with sodium bicarbonate, and an outer core of omeprazole enterically coated granules mixed with known binders and excipients. It is clear from *Phillips* that the described omeprazole powder and sodium bicarbonate form one (a **first**) population. The omeprazole powder and sodium bicarbonate are uniformly mixed and, as described later in Example VI, the inner core is disbursed in the stomach where it is absorbed for immediate therapeutic effect, while the **second** population of the enterically coated granules are later absorbed in the duodenum. Thus, Example VI of *Phillips* pertains to a **single** population of granules, namely the enterically coated granules, and clearly does ***not*** describe **four** populations each being a population of beads, of pellets, of tablets, of granules, ***or*** a combination thereof as recited in claim 31 of the present application, as herein amended.

Bergstrand has only been relied upon for disclosing a separating layer and, for at least this reason, does not overcome the deficiencies of *Phillips* with respect to the Examiner's obviousness objection. While *Bergstrand* may teach that an alkaline layer between a PPI and an enteric coat may protect the PPI, Applicants fail to see how this relates to the contents of the capsules of the claims of the present application. Therein, the contents include a population of enteric coated PPI **granules, tablets, pellets, or beads.** Only **this** component of the presently claimed capsule preparations equates in any way with the PPI preparations as taught by *Bergstrand*, that requires an alkaline layer when the PPI is enterically coated. The teachings of *Bergstrand* do **not** relate in any way to the **individual** PPI and basic substance populations of the presently claimed formulations, which are individually **granules, tablets, pellets, or beads.**

Moreover, it is asserted that although *Bergstrand* was not relied upon for teaching a capsule structure, the fact that *Bergstrand* clearly teaches away from the use of a capsule would fail to motivate a skilled person to use a capsule as is presently claimed. This teaching away from a capsule would also lead a skilled person towards the use of other formulations such as a tablet, and away from the claimed subject matter of the present application. The Examiner cannot pick and choose which teachings a skilled person would rely upon from the prior art and which teachings he would disregard. A hindsight claim analysis should be avoided, since it is easy to allege obviousness once the solution to a problem is explained.

Applicants, therefore, assert that the cited references of *Phillips* and *Bergstrand*, for at least the above reasons, do not teach, individually or in combination, the encapsulated formulations comprising four substance populations as claimed in claim 31 as amended herein, and in claims 32-48 dependent therefrom. Applicants, therefore, respectfully request that this rejection under 35 USC §103(a) be withdrawn.

Applicants assert, therefore, that (i) the cited reference of *Bergstrand* specifically teaches away from the use of capsules such as those of *Phillips*; (ii) there is no statement or teaching in the *Phillips* reference that can provide any motivation for combining the compositions as described by *Phillips* with those as taught by *Bergstrand* to arrive at the compositions as claimed in the present application; (iii) the Examiner has failed to meet a *prima facie* case of obviousness by merely stating an assumption that one of ordinary skill in the art would be motivated to combine *Phillips* and *Bergstrand* without providing any explanation as to why.

In this regard, the MPEP section 2141 states:

> "The Supreme Court in KSR reaffirmed the familiar framework for determining obviousness as set forth in Graham v. John Deere Co. (383 U.S. 1, 148 USPQ 459 (1966))... As reiterated by the Supreme Court in KSR, the framework for the objective analysis for determining obviousness under 35 U.S.C. 103 is stated in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966). Obviousness is a question of law based on underlying factual inquiries. The factual inquiries enunciated by the Court are as follows:
>
> (A) determining the scope and content of the prior art;
>
> (B) Ascertaining the differences between the claimed invention and the prior art; and
>
> (C) Resolving the level of ordinary skill in the pertinent art.

In addition:

> When applying 35 U.S.C. 103, the following tenets of patent law must be adhered to:
>
> (A) The claimed invention must be considered as a whole;
>
> (B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;
>
> (C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention and
>
> (D) Reasonable expectation of success is the standard with which obviousness is determined.
>
> Hodosh v. Block Drug Co., Inc., 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986)."

As reflected above, the foregoing approach to obviousness determinations was recently confirmed by the United Stated Supreme Court decision in KSR INTERNATIONAL CO. V. TELEFLEX INC. ET AL. 550 U.S. 1, 82 USPQ2d 1385, 1395-97 (2007), where the Court stated:

> "In Graham v. John Deere Co. of Kansas City, 383 U. S. 1 (1966), the Court set out a framework for applying the statutory language of §103, language itself based on the logic of the earlier decision in Hotchkiss v. Greenwood, 11 How. 248 (1851), and its progeny. See 383 U. S., at 15–17. The analysis is objective:
>
> "Under §103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or non-obviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." Id., at 17–18."

Indeed, as now expressly embodied in MPEP 2143, "[t]he ***key to supporting any rejection under 35 U.S.C. §103 is the clear articulation of the reason(s) why the claimed invention would have been obvious***. The Supreme Court in KSR noted that the analysis supporting a rejection under 35 U.S.C. §103 should be made explicit." (*Emphasis added, MPEP 2143*). "Objective evidence relevant to the issue of obviousness ***must*** be evaluated by Office personnel." (MPEP 2141). "The key to supporting any rejection under 35 U.S.C. §103 is the ***clear articulation of the reason(s)*** why the claimed invention would have been obvious. The Supreme Court in KSR noted that the analysis supporting a rejection under 35 U.S.C. §103

should be made explicit. The Court quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), stated that '[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." (MPEP 2141).

Applicants acknowledge that the reliance on an excessive number of references, by itself, may not weigh against the obviousness of the claimed invention. *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991). The same court espoused that "it is impermissible, however, simply to engage in a hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps." Further, the "references themselves must provide some teaching whereby the applicant's combination would have been obvious." Thus, without the indication provided by Applicants, "picking and choosing" components from a number of references merely to meet the features of the claims of the present application is substantially improper "hindsight".

The alleged rationale for combining the references is merely an improper ***conclusory*** statement that embodies clear and improper hindsight rationale, and still does not arrive at the combination of elements as claimed in the amended claims submitted herein.

Applicants, therefore, respectfully request that this rejection under 35 USC §103(a) be withdrawn.

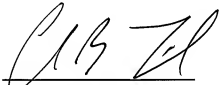
CONCLUSION

In light of the foregoing amendments and for at least the reasons set forth above, Applicants respectfully submit that all objections and/or rejections have been traversed, rendered moot, and/or accommodated, and that the now pending claims are in condition for allowance. Favorable reconsideration and allowance of the present application and all pending claims are hereby courteously requested.

Any other statements in the Office Action that are not explicitly addressed herein are not intended to be admitted. In addition, any and all findings of inherency are traversed as not having been shown to be necessarily present. Further, any and all findings of well-known art and official notice, or statements interpreted similarly, should not be considered well known for at least the specific and particular reason that the Office Action does not include specific factual findings predicated on sound technical and scientific reasoning to support such conclusions.

If, in the opinion of the Examiner, a telephone conference would expedite the examination of this matter, the Examiner is invited to call the undersigned attorney at (770) 933-9500.

Respectfully submitted,



Christopher B. Linder
Registration No. 47,751

THOMAS, KAYDEN, HORSTEMEYER & RISLEY, L.L.P.
Suite 1500
600 Galleria Parkway N.W.
Atlanta, Georgia 30339
(770) 933-9500